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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/297,877	06/28/1999	VIRGINIA M.-Y. LEE	PENN-0583	1398

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EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/297,877	LEE ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 4 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 4 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 06 March 2003 (Paper No. 20) has been entered in full.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 4 is under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objection to the specification at pg 2-3 of the previous Office Action (Paper No. 18, 06 November 2003) is *withdrawn* in view of the amended title (Paper No. 20, 06 March 2003).

Claim Rejections - 35 USC § 112

2. Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis for this rejection is set forth at pg 3-6 of the previous Office Action (Paper No. 18, 06 November 2002).

Specifically, claim 4 recites a method of inhibiting the processing of amyloid precursor protein into amyloid β peptides found in neuritic plaques and vascular deposits that accumulate in the brains of patients with Alzheimer's disease comprising administering to a patient an agent which decreases processing of amyloid precursor protein into amyloid β peptides wherein said agent is identified by (i) contacting NTN2 cells with the agent and (ii) measuring levels of amyloid β peptides formed in the endoplasmic reticulum (ER) of the cells.

Applicant's arguments (Paper No. 20, 06 March 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that as well known to those of skill in the art, the NT2N cell model system is a predictable system used to study APP processing in neurons. Applicant states that NT2N cells have been reported to produce intracellular Aβ. Applicant argues at pg 7 of the Response that there is more than a reasonable correlation between the activity taught in the specification and the asserted method of claim 4. Applicant contends that based upon the teachings of the instant invention, one of skill in the art would routinely be able to administer an agent which decreases processing of amyloid precursor protein into amyloid β peptides, such as those found in neuritic plaques of Alzheimer patients. Applicant asserts that the demonstrated efficiency of the claimed method of contacting NT2N cells with an agent suspected of decreasing amyloid precursor protein processing to inhibit the processing of amyloid precursor protein into amyloid β peptides, in the specification is clearly suggestive to one skilled in the art that the claimed method would work in a patient.

Applicant's arguments have been fully considered but are not found to be persuasive. The specification of the instant application outlines a prophetic procedure for treating Alzheimer's disease with an agent that inhibits the processing of amyloid precursor protein into amyloid β peptides (pg 4, lines 29-37 through pg 5, lines 1-9). However, this disclosed suggestion and the *in vitro* experiments with NT2N cells (pg 9-10) is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors

such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily inhibit the processing of amyloid precursor protein into amyloid β peptides in patients with Alzheimer's disease by administration of an agent that decreases said processing. Although part of the claimed method utilizes routine agent identification techniques, the results of the method are unpredictable and complex when combined with the step of administering the agent identified to a patient with Alzheimer's disease. Also, although the NT2N model system is a predictable system used to study APP processing in neurons, it is not an art recognized model system for Alzheimer's disease. Therefore, one skilled in the art would not predict from the guidance in the specification that an agent that decreases amyloid precursor protein processing in the NT2N model system would necessarily decrease amyloid precursor protein processing in a patient.

Furthermore, as discussed in the previous Office Action, the skilled artisan must resort to trial and error experimentation to determine the optimal dosage, duration, and mode of administration of all possible agents. Since the specification provides no guidance regarding what sort of agents should be screened for inhibiting the processing of amyloid precursor protein, the skilled artisan must resort to trial and error experimentation to determine which class of compounds might yield one with the desired activity. Such trial and error experimentation is considered undue.

(ii) Applicant disagrees with the characterizations of Brinton et al. and Roses and their relevance in light of the 35 U.S.C. § 112, first paragraph rejection. It is noted that these references were cited by the Examiner in the previous Office Action (Paper No. 18, 06 November 2002). Applicant also states that in accordance with MPEP 2107.01, office personnel should be especially careful not to read into a claim unclaimed results, limitations or embodiments. Applicant indicates that claim 4 is drawn to a specific methods of inhibiting the processing of amyloid precursor protein into amyloid β peptides. Applicant contends that the Examiner has inappropriately read into claim 4, unclaimed results, limitations or embodiments of an invention. Applicant asserts that none of the recited art addresses modulation of the processing of amyloid precursor protein into amyloid β peptides.

Applicant's arguments have been fully considered but are not found to be persuasive. The fact patterns of the section of the MPEP and cases cited by the Applicant are significantly different, and the court decisions are not binding with regard to the instant rejections. Specifically, MPEP 2107 and the recited court decisions discuss utility rather than the issue at hand in the instant application, which is total lack of enablement. Additionally, the references cited by the Examiner in the previous Office Action (Brinton et al. and Roses) are intended to indicate the state of the art at the time the invention was made. As mentioned previously, for example, cholinergic pharmaceuticals only modestly improve cognitive function, have short-lived effects, and are in the early stage of development (Brinton et al., Pharmaceutical Res 15(3): 386-398, 1998, pg 393, col 2, ¶ 4 through pg 394). Brinton et al. also mentions that unlike animal studies with NGF, human trials have not been successful (pg 394, col 1). Additionally, Roses (Lancet 355: 1358-1361, 2000) discloses that "if an effective treatment were to be

developed for a common form of the illness, it might not work for all patients, especially those with rare mutational forms of Alzheimer's disease. Conversely, a treatment developed for a specific mutation may have no effect in common Alzheimer's phenotypes" (pg 1358, bottom of col 1 through top of col 2). Roses also states that a patient's response to a drug may depend on other factors than the alleles the individual carries, such as drug distribution, drug absorption, drug concentration at the target site, and drug metabolism and elimination (pg 1358, col 2, ¶ 1).

Brinton et al. and Roses are not reading unclaimed results or limitations into claim 4. It is noted that claim 4 essentially has two main steps recited. The first step is identifying an agent that decreases the processing of amyloid precursor protein into amyloid β peptides and the second is step is actually administering this agent to patients with Alzheimer's disease (AD) to inhibit the processing of amyloid precursor protein into amyloid β peptides found in neuritic plaques and vascular deposits that accumulate in the brain. Therefore, claim 4 does read upon administering an agent to an AD patient. Brinton et al. and Roses are pertinent references since they comment on the status of AD treatment at the time the application was filed. Overall, these references simply indicate that Alzheimer's disease is recalcitrant to treatment, that there is no cure for Alzheimer's disease, and that only recently have therapeutic *strategies* emerged. One of skill in the art would not be able to predict inhibition of the processing of amyloid precursor protein into amyloid β peptides in AD patients by administration of an agent because AD is difficult to treat and there is no guidance in the specification with respect to the type of agent to be administered and the optimal dosage, duration, and mode of administration.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to identify an agent that decreases processing of

amyloid precursor protein and to determine the optimal dosage, duration, and mode of administration of all possible agents to a patient, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art, and the unpredictability of the effects of inhibiting the processing of amyloid precursor protein into amyloid β plaques *in vivo*, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

Claim 4 is not allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
June 3, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER